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ALIMENTARY TRACT

Utility of Testing Patients, on Presentation, for Serologic Features of Celiac Disease

Melpakkam Srinivas,* Pandurangan Basumani,* Geoff Podmore,‡ Anna Shrimpton,‡ and Karna Dev Bardhan*

*Department of Gastroenterology and ‡Department of Immunology, The Rotherham NHS Foundation Trust, Rotherham, South Yorkshire, United Kingdom

BACKGROUND & AIMS: **Celiac disease shares features of other disorders. It can be diagnosed conclusively only based on duodenal histology analysis, which is not practical for screening purposes. Serologic analysis might be used to identify candidates for biopsy analysis. We aimed to develop a simple diagnostic approach that all clinicians could follow to increase the percentage of patients accurately diagnosed with celiac disease at initial presentation.**

METHODS: **We performed a retrospective analysis of data from 752 patients (88 with celiac disease, none were IgA deficient) who attended a UK district general hospital from January 2007 through December 2008 and underwent biopsy analysis and serologic tests to measure endomyseal antibodies and IgA antibodies against tissue transglutaminase (tTG). Patients avoiding gluten in their diet were excluded. Patients were assigned to 1 of 4 groups: high-risk (based on presence of anemia, chronic diarrhea, unintentional weight loss, or dermatitis herpetiformis), low-risk (based on such factors as dyspepsia, abnormal liver function, ataxia, or chronic cough), nutrient deficiency (based on levels of iron, vitamins B_{12} and D, or folate), or screening (because they had type 1 diabetes or a family history of celiac disease). Patients with celiac disease were identified using the modified Marsh criteria (grades 1–3) for interpreting duodenal histology. We compared clinical category, serology profiles, and biopsy results between patients with and without celiac disease.**

RESULTS: **Celiac disease was diagnosed in 64 of 565 patients in the high-risk group (11%), 14 of 156 patients in the low-risk group (9%; $P = .47$ compared with high-risk group), 7 of 28 patients in the nutrient-deficiency group, and 3 of 3 patients in the screening group. Among 71 patients who tested positive for both antibodies (tTG and endomyseal antibodies), the positive predictive value for celiac disease was 97%; a negative test result for tTG had a negative predictive value of 98%. Among 708 patients with normal-looking biopsy samples, only 62 had celiac disease (9%). Among 44 patients with abnormal biopsy samples, 26 had celiac disease (59%).**

CONCLUSIONS: **Based on a retrospective analysis, patients with and without celiac disease cannot be distinguished based on clinical features. Patients who present with symptoms of celiac disease should be tested for tTG, to identify candidates for duodenal biopsy analysis.**

Keywords: Algorithm; Diagnostic Test; Gluten Allergy; Antibody.

Celiac disease (CD) is prevalent in approximately 1% of whites[1–7] and those affected manifest a wide spectrum of classical and nonspecific features. However, many more have similar clinical problems but without CD. The distinction is important to make because although CD can be effectively treated with gluten-free diet (GFD), using the gold standard of diagnosis (ie, histology, by identification of typical histologic changes in endoscopic biopsies from the second part of duodenum [D2]) is impractical in view of the large number of people in whom CD needs to be considered. These factors coupled with the general lack of awareness until recently of the spectrum of CD manifestations perhaps explain the previously reported median delay of up to 11 years[8–10] to make the diagnosis.

Abbreviations used in this paper: CD, celiac disease; D2, second part of duodenum; EMA, antiendomysial antibody; GFD, gluten-free diet; GI, gastrointestinal; IgA, immunoglobulin A; IgG, immunoglobulin G; NPV, negative predictive value; PPV, positive predictive value; tTG, anti–tissue transglutaminase.

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We started using celiac serology as a screening tool in the 1990s in our center (UK district general hospital serving a population of about 250,000) to identify those most likely to have CD and perform D2 biopsy in this smaller number. The four-antibody screening panel used was immunoglobulin A (IgA) and immunoglobulin G (IgG) antigliadin, IgA antireticulin, and IgA anti-endomysial antibodies (EMA). A decade later we found that, uncertain of their sensitivity and specificity in the circumstances of our clinical practice, clinicians in our hospital interpreted the results as being suggestive of CD only if at least 3 of the 4 tests were positive. This resulted in instances when if EMA was the only antibody positive, it was disregarded despite it being a specific marker of CD. With growing evidence establishing IgA anti–tissue transglutaminase (tTG) as a sensitive marker of CD,[11] we switched to a "less is more" strategy of using only IgA tTG and IgA EMA in the screening panel from mid-2006.

We reviewed our data since this change to assess if, from the evidence gathered, we could develop a simple pragmatic strategy that all clinicians could follow in a systematic manner across all disciplines when evaluating a patient for possible CD, with the aim of "maximizing hit yet minimizing miss" at initial presentation.

Patients, Materials, and Methods

All patients attending our center in a 2-year period (January 2007 to December 2008) who had seroscreening or duodenal histology to exclude CD were identified from the hospital immunology and histology databases.

Inclusion and Exclusion Criteria

Patients with serology (both IgA tTG and IgA EMA) and D2 histology checked within 6 months of each other (irrespective of which test was done first) were included in the study. Patients tested while on GFD were excluded.

Additional Patient Information

Information was obtained from respective databases, reporting software, and other sources and included presenting symptoms and relevant HLA status (if done) from case notes and clinic letters, blood tests from DM Nurse (pathology-reporting software), D2 appearances of CD (ie, scalloping, nodularity, flatness, if described, from endoscopy reports), and histology from H-Lab (histology-reporting software).

Clinical Categories

Patients were categorized by their clinical features into 4 clinical groups. (1) High risk, as defined by the British Society of Gastroenterology guidelines[12]: anemia, chronic diarrhea, and unintentional weight loss, to which we added dermatitis herpetiformis,[13] these being the "classical" features of CD. (2) Low risk, subdivided into gastrointestinal (GI) and non-GI. GI included nonspecific abdominal pain,[14] gastroesophageal reflux,[15,16] dyspepsia, and unexplained abnormal liver function tests; non-GI included tiredness, ataxia,[17] chronic cough,[18] and osteoporosis.[19,20] (3) Nutrient deficiencies (iron, vitamins B_{12},[21] and D, or folate deficiencies). (4) Screening for type 1 diabetes[22] and family history (all in this group had serology first, with subsequent D2 biopsy only if serology was positive).

Interpretation of D2 Biopsies

The modified Marsh criteria[23–26] were used to categorize the histology findings as follows: grade 0 = normal, grade 1 = raised intraepithelial cell lymphocyte count, grade 2 = grade 1 plus crypt hyperplasia, grade 3a = grade 1 plus 2 plus partial villous atrophy, grade 3b = grade 1 plus 2 plus subtotal villous atrophy, grade 3c = grade 1 plus 2 plus total villous atrophy. Those with Marsh grade 1–3 were deemed to have histology suggestive of CD.

Serology Assays

IgA tTG was measured with Organtec Alegria using Organtec ELISA reagents (Orgentec Diagnostika GmbH, Mainz, Germany). Values <10 IU/mL were classed as normal. IgA EMA was performed by indirect immunofluorescence on Biosystems antiendomysium (monkey esophagus) slides (Biosystems S.A, Barcelona, Spain); results were reported as negative, weak positive, or positive. The tTG assay was automated, whereas the EMA detection was manual. IgA was measured turbidimetrically on Siemens Advia 1800 (Seimens Healthcare Diagnostics Ltd, Camberley, United Kingdom).

Analyses and Statistics

The following were compared in patients with CD versus without CD in each of the 4 clinical groups: clinical features, serology profile, and duodenal macroscopic appearance. We examined tTG results when expressed simply as positive (tTG >10 IU/mL) or negative, and its relation with EMA strengths of seropositivity (positive or weak positive).

The "seronegative CD" subgroup, based on histology fulfilling modified Marsh criteria, was compared with the seropositive CD group for discriminant clinical features, endoscopic appearances, and outcome of a trial of GFD if used.

Sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) for the serology tests, and P values by Fisher exact test or Wilcoxon signed rank sum test, where appropriate, were calculated.

The study was approved by the institution's clinical effectiveness department as a service improvement project.